Research progress on autophagy mediated by molecular chaperone and colorectal cancer

Yaping He[a], Haiyan Peng[b,*]

Nanjing University of Chinese Medicine, Najing, 210023, Jiangsu, China

[a]1848755948@qq.com, [b]260615@njucm.edu.cn

*Corresponding Author

Keywords: colorectal cancer; autophagy; molecular chaperone

Abstract: Colorectal cancer, a prevalent condition, has garnered significant scientific and clinical focus. In the past few years, autophagy—a pivotal cellular process facilitated by molecular partners—has become a research hotspot due to its critical role in colorectal cancer's progression, therapeutic responses, and drug resistance. This article reviews advances in understanding the interplay between autophagy and colorectal cancer, highlighting promising future research avenues. Initially, we delve into the roles played by molecular chaperones, specifically HSP70, HSP90, and CHIP, in colorectal cancer biology. Subsequently, we underscore the significance of autophagy in colorectal cancer treatment paradigms. Lastly, we explore future research prospects, such as the tailoring of personalized treatment strategies, the development of drugs that modulate autophagy, and the translation of these research findings into clinical practice. The intersection of molecular chaperone-mediated autophagy and colorectal cancer research represents a dynamic and rapidly evolving field. By deepening our understanding of the interplay between molecular chaperones and autophagy, we anticipate developing more effective therapeutic strategies, thereby enhancing outcomes for patients with colorectal cancer and expanding their health and survival prospects.

1. Introduction

Autophagy, specifically the subtype known as Chaperone-mediated autophagy (CMA), has garnered significant interest within the realm of tumor biology. This cellular self-degradation process serves a crucial function in maintaining the intracellular balance by breaking down damaged or unneeded organelles and proteins into their basic building blocks. While autophagy plays a pivotal role in normal cellular functions, its involvement in tumor development and progression is complex and multifaceted. Colorectal cancer, a prevalent and often fatal malignancy, underscores the importance of understanding autophagy's role in cancer pathogenesis and treatment.

Within the autophagy umbrella, macroautophagy (MA), microautophagy (MI), and CMA differ in their mechanisms of delivering cargo to the lysosome. CMA is unique in its reliance on cytosolic chaperones to selectively identify and target substrates for lysosomal degradation. This pathway involves specialized proteins called molecular chaperones, which are adept at recognizing, binding, and transporting specific cellular components destined for destruction. Their primary function is to aid in the proper folding, stabilization, and transport of other proteins.

In the context of CMA, these chaperones play a pivotal role in substrate selection. They interact with specific proteins or organelles marked for degradation [1], a feature that distinguishes CMA from other autophagy pathways [2]. Once bound to their target, the chaperones form a complex that is guided to the lysosome, ensuring efficient delivery of the cargo. Within the lysosome, the complex dissociates, releasing the substrate to be broken down by degradative enzymes [3]. These enzymes then recycle the components for cellular reuse or elimination [4]. This selective degradation process mediated by molecular chaperones is critical for maintaining cellular homeostasis and responding to stress.

Our focus in this review is on the intricate relationship between molecular chaperones and autophagy, with a particular emphasis on their implications in colorectal cancer. We delve into how

  DOI: 10.25236/icetmr.2023.033

specific chaperones like LAMP2A, HSC 70, and HSP 90 regulate autophagy and their expression patterns and functionalities within colorectal cancer cells. Furthermore, we explore the potential therapeutic applications of chaperone-mediated autophagy in colorectal cancer treatment, including strategies that involve manipulating the autophagy pathway via molecular chaperones.

Advancements in this area promise to shed new light on the pathophysiological mechanisms underlying colorectal cancer and to pave the way for innovative treatment strategies. By unpacking the role of chaperone-mediated autophagy in colorectal cancer, we aim to contribute to the development of more effective therapies, ultimately improving the survival rates and quality of life for patients battling this devastating disease.

2. The basic concept of autophagy

Autophagy, a crucial intracellular self-degradation process, plays a pivotal role in sustaining the intracellular environment's homeostasis and eliminating damaged or superfluous cellular elements. This tightly controlled biological phenomenon comes in various forms, namely macroautophagy, microautophagy, and CMA (Chaperone-mediated autophagy).

(1) Macroautophagy overview

Macroautophagy, the most extensively explored autophagy variety, involves the formation of a double-membrane autophagosome. This structure encapsulates proteins, organelle fragments, and additional cellular constituents, ultimately merging with lysosomes for degradation.

(2) Microautophagy essentials

Microautophagy, while less studied, involves the lysosomal membrane's direct phagocytosis of target proteins or organelles. Unlike macroautophagy, it doesn't require autophagosome formation, instead relying on direct ingestion of the desired substance.

(3) CMA fundamentals

CMA is a highly selective autophagy pathway crucial for the degradation and recycling of specific cellular components. It relies on molecular chaperones, proteins specialized in recognizing, transporting, and degrading designated target proteins.

CMA's selectivity is remarkable, targeting specific proteins for degradation based on the KFERQ-like motif, rather than non-specific bulk degradation. Molecular chaperones like Hsc70 are instrumental in this process, recognizing the KFERQ-like motif and aiding in the proteins' delivery to lysosomes.

Once chaperones identify the substrate proteins, they're transported to lysosomes. Here, lysosomal-associated membrane protein type 2A (LAMP-2A), a vital CMA translocation complex component, facilitates their translocation into the lysosomal lumen.

LAMP-2A functions as a receptor for these proteins at the lysosomal membrane. The substrate is then unfolded and moved across the membrane into the lysosomal lumen, where proteases like cathepsins break it down into amino acids. CMA is tightly regulated, responding to cellular stress, nutrient levels, and other external cues. This selectivity is critical for maintaining cellular health by eliminating damaged or unneeded proteins.

Disruptions in CMA have been linked to diverse pathologies, including neurodegenerative diseases, cancer, and metabolic disorders [5]. Unraveling CMA's molecular mechanisms offers promise for developing targeted therapeutic approaches.

In conclusion, Chaperone-Mediated Autophagy represents a sophisticated and selective cellular process that contributes significantly to the maintenance of cellular health and function. Its intricate regulatory mechanisms and involvement in various diseases make it a subject of active research in cell biology and potential therapeutic interventions.

(4)Physiological and pathological functions of molecular CMA

CMA selectively degrades certain proteins, playing a crucial role in cellular homeostasis. This intricate process impacts cell function both physiologically and pathologically. CMA promotes cell health by degrading proteins that are damaged or incorrectly folded, thus ensuring protein quality and preventing harmful protein clumps [6]. When nutrients are scarce or cells are stressed, CMA becomes crucial for survival as it breaks down proteins to recycle amino acids, aiding in energy

balance and nutrient supply. Additionally, CMA regulates cell signaling by degrading key proteins, affecting cell differentiation, growth, and responses to the environment. It's also involved in cellular senescence regulation, potentially influencing aging and cell lifespan by degrading senescence-related proteins.

Disruptions in CMA have been tied to neurodegenerative diseases like Alzheimer's, Parkinson's, and Huntington's. When CMA doesn't function properly, misfolded and clumped proteins accumulate, hallmarks of these diseases. Altered CMA activity has also been noted in various cancers. Both increased and decreased CMA activity have been linked to cancer development, indicating a multifaceted role in tumorigenesis and a possible impact on the balance between cancer cell survival and death.

Grasping CMA's delicate balance in healthy and diseased states paves the way for potential therapies. Targeting CMA could lead to new treatments for neurodegenerative diseases, cancer, and metabolic disorders by fine-tuning protein degradation and cellular homeostasis.

3. Application of autophagy mediated by molecular chaperone in the treatment of colorectal cancer

3.1. Potential application

Colorectal cancer is a common type of cancer, and its morbidity and mortality are still quite high worldwide. The existing treatments include surgery, radiotherapy and chemotherapy, but these treatments have certain limitations, especially for advanced patients. Therefore, researchers have been exploring new therapeutic strategies, and the autophagy mechanism mediated by molecular partners has increasingly become one of the focuses.

Molecular chaperones, notably HSP70, HSP90, and CHIP, assist proteins in correct folding, stability maintenance, and degradation when required. Their connection with autophagy has sparked interest in their potential for colorectal cancer treatment [7-8].

These chaperones, including HSP70 and HSP90, modulate autophagy pathway activation by influencing the folding and activity of related proteins. This offers a novel autophagy intervention approach. By adjusting chaperones, we can selectively intervene in autophagy pathways, controlling autophagy's extent and timing in cells. Autophagy pathway activation often correlates with tumor cell drug resistance. Chaperone-mediated autophagy can diminish this activity, sensitizing tumor cells to therapies [9]. Combining chaperone regulation with traditional radiotherapy and chemotherapy might enhance treatment effectiveness, especially for drug-resistant tumors. Moreover, proper autophagy regulation can mitigate radiotherapy and chemotherapy side effects, making treatment more tolerable and improving patients' quality of life.

LAMP2A, a lysosome-associated membrane protein, plays a pivotal role in autophagy, a cellular self-degradation process eliminating damaged or obsolete proteins and organelles. LAMP2A functions as a rate-limiting molecule, mediating autophagy formation and degradation.

Molecular chaperones, proteins that aid in the correct folding, assembly, and stability of other proteins [11], can also interact with autophagy-related proteins like LAMP2A, modulating autophagy. As a key player in autophagy, LAMP2A's role in formation and degradation is influenced by chaperones regulating its function.

Delving into chaperone-mediated autophagy can reveal new anticancer drug targets. Specific chaperone-mediated autophagy pathways are research focal points, promising new drug discoveries [12]. However, chaperone-mediated autophagy's effects vary across cells and tumors, necessitating further experimental studies to elucidate its mechanisms and potential in colorectal cancer treatment. Clinical trials and translational research are crucial for assessing these concepts' feasibility and efficacy in patients.

In summary, chaperone-mediated autophagy offers promising potential in colorectal cancer treatment. Modulating autophagy pathways can enhance treatment effectiveness, reduce side effects, and guide new drug development, bringing hope to colorectal cancer patients. Future research in this area aims to refine treatment strategies, improving patient survival and quality of life.

3.2. Interventions against autophagy mediated by molecular chaperone

Radiotherapy is a method commonly used in cancer treatment, which irradiates tumor tissue with high-energy rays and damages its DNA structure, thus inhibiting tumor growth. However, some tumor cells can resist radiation-induced damage by autophagy. Therefore, researchers began to explore how to improve the efficacy of radiotherapy by inhibiting autophagy.

Chemotherapy is a treatment that uses drugs to kill or inhibit the growth of cancer cells. Some chemotherapeutic drugs can induce autophagy, which may help to degrade toxic metabolites in cancer cells in some cases. However, excessive autophagy may lead to drug resistance, so researchers are also looking for appropriate ways to inhibit autophagy.

HSP90 inhibitors are a kind of drugs, which block the interaction between HSP90 and guest protein by inhibiting its activity. These drugs have been studied for cancer treatment because HSP90 is related to the stability and folding of many tumor-related proteins. By interfering with the interaction between HSP90 and autophagy-related proteins, these drugs may affect autophagy pathway. In recent years, researchers have identified some autophagy inhibitors, including Chloroquine and Hydroxychloroquine. These drugs can block the autophagy process, thus enhancing the efficacy of cancer treatment. In addition, some studies have also explored new autophagy inhibitors to more selectively interfere with autophagy pathway[12].

Drug research on molecular chaperones is also under way. These drugs aim to influence the interaction between molecular chaperones and autophagy-related proteins, so as to change the regulation and activity of autophagy. The research in this field may provide new ideas for developing more targeted treatment strategies.

The existing therapeutic strategies and drugs, including the intervention measures of autophagy mediated by molecular partners, have potential applications in the treatment of cancer and other diseases. The development of these strategies and drugs provides a new way to improve the therapeutic effect of patients, especially by regulating autophagy pathway, which is expected to improve the curative effect of radiotherapy and chemotherapy and reduce the side effects of treatment. Future research will further promote the development of these fields in order to improve the survival rate and quality of life of patients.

4. Research prospect and future direction

Colorectal cancer, a prevalent malignancy globally, has garnered significant attention due to its alarmingly high incidence and mortality rates. The prospect of exploring autophagy, mediated by molecular chaperones, holds promise in advancing colorectal cancer research. Specifically, the involvement of molecular chaperones, including HSP70, HSP90, and CHIP, in this malignancy has piqued research interest. These chaperones are crucial for maintaining protein stability, folding, and degradation, and their link to cancer progression and treatment resistance has been observed.

Future inquiries will delve deeper into the role of autophagy in colorectal cancer's treatment resistance. Unraveling how autophagy aids cancer cells in evading treatment's impact could pave the way for innovative therapeutic approaches aimed at enhancing treatment efficacy. With the in-depth study of autophagy mediated by molecular chaperone, it is expected to develop individualized treatment strategies and choose the best treatment scheme according to the characteristics of molecular chaperone and autophagy status of patients. It is a potential field to further develop autophagy regulating drugs, such as HSP90 inhibitors and autophagy inhibitors, and new molecular chaperone intervention drugs for the treatment of colorectal cancer.

Combining autophagy regulating drugs with traditional radiotherapy and chemotherapy or new immunotherapy may improve the therapeutic effect of colorectal cancer patients. Studying the biomarkers of molecular chaperones and autophagy can help monitor the disease progress and treatment response, and predict the prognosis of patients. By translating autophagy mediated by molecular chaperone into clinical practice, it is expected to provide more effective treatment options for colorectal cancer patients.

Molecular chaperone mediated autophagy provides a broad prospect and future direction for the

treatment of colorectal cancer. Further discussion on the interaction between molecular chaperone and autophagy, development of autophagy regulating drugs and development of individualized treatment strategies may bring better treatment results for patients with colorectal cancer. Future research and clinical practice will further promote the development of this field and improve the survival rate and quality of life of patients with colorectal cancer.

5. Conclusions

Colorectal cancer is a high-incidence disease, and the research on its treatment strategy and mechanism has always been concerned. As an important cell biological process, autophagy mediated by molecular chaperone has shown great potential in the study of colorectal cancer. By studying the interaction between autophagy and molecular chaperones such as HSP70, HSP90 and CHIP, we can better understand the complex mechanism in the development and treatment of colorectal cancer. Molecular chaperone-mediated autophagy has made remarkable progress in colorectal cancer research. Future research will further deepen our understanding of this field and bring new hope for colorectal cancer treatment. By continuing to promote the research and application in this field, we are expected to improve the therapeutic effect of patients with colorectal cancer and provide more opportunities for their health and survival.

Acknowledgements

The authors acknowledge the Jiangsu Provincial Natural Science Foundation Project: “Exploring the Mechanism of the Xianhecao-Huanglian Drug Pair in Intervention of Colorectal Inflammation and Cancer Transformation Based on Regulating CMA to Maintain Intestinal Mucosal Steady State.” (NO:BK20201400)

References

[1] Tekirdag, K., & Cuervo, A. M. (2018). Chaperone-mediated autophagy and endosomal microautophagy: jointed by a chaperone. The Journal of biological chemistry, (15), 293.

[2] Chen, J., Yang, Y., Russu, W. A., & Chan, W. K. (2021). The aryl hydrocarbon receptor undergoes chaperone-mediated autophagy in triple-negative breast cancer cells. International Journal of Molecular Sciences, 22(4), 1654.

[3] Rose, J. M., Novoselov, S. S., Robinson, P. A., & Cheetham, M. E. (2011). Molecular chaperone-mediated rescue of mitophagy by a parkin ring1 domain mutant. Human Molecular Genetics, 20(1), 16-27.

[4] Orenstein, S. J., & Cuervo, A. M. (2010). Chaperone-mediated autophagy: molecular mechanisms and physiological relevance. Seminars in Cell and Developmental Biology, 21(7), 719-726.

[5] Lee, Y. H., & Bottaro, D. P. (2013). Abstract 4285: hypoxia-mediated autophagy enhances hgf-induced cancer cell invasion. Cancer Research, 73(8), 4285-4285.

[6] Ramos, A., & Hemann, M. T. (2017). Drugs, bugs, and cancer: fusobacterium nucleatum promotes chemoresistance in colorectal cancer. Cell, 170(3), 411-413.

[7] Cloutier, P., & Coulombe, B. (2013). Regulation of molecular chaperones through post-translational modifications: decrypting the chaperone code. Biochimica Et Biophysica Acta, 1829(5), 443-454.

[8] Hammack, L. J., Firestone, K., Chang, W., & Kusmierczyk, A. R. (2017). Molecular chaperones of the hsp70 family assist in the assembly of 20s proteasomes. Biochemical & Biophysical Research Communications, 486(2), 438-443.

[9] Xia, H. G., Najafov, A., Geng, J., Galan-Acosta, L., & Vakifahmetoglu-Norberg, H. (2015).

Degradation of hk2 by chaperone-mediated autophagy promotes metabolic catastrophe and cell death. The Journal of Cell Biology, 210(5), 705-716.

[10] Gorantla, N. V., & Chinnathambi, S. (2018). Tau protein squired by molecular chaperones during alzheimer's disease. Journal of Molecular Neuroscience, 66(3), 356-368.

[11] Lai, K., Killingsworth, M. C., & Lee, C. S. (2014). The significance of autophagy in colorectal cancer pathogenesis and implications for therapy. Journal of Clinical Pathology, 67(10), 854- 858.

[12] Rothenberg, C., Srinivasan, D., Mah, L., Kaushik, S., Peterhoff, C. M., & Ugolino, J., et al. (2010). Ubiquilin functions in autophagy and is degraded by chaperone-mediated autophagy. Human Molecular Genetics, 19(16), 3219.